

# BMJ Open Comparative efficacy of selective serotonin reuptake inhibitors (SSRI) in treating major depressive disorder: a protocol for network meta-analysis of randomised controlled trials

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## ABSTRACT

**Introduction:** There have been inconsistent findings from randomised controlled trials (RCTs) and systematic reviews on the efficacies of selective serotonin reuptake inhibitors (SSRIs) as the first-line treatment of major depressive disorder (MDD). Besides inconsistencies among randomised controlled trials (RCTs), their risks of bias and evidence grading have seldom been evaluated in meta-analysis. This study aims to compare the efficacy of SSRIs by conducting a Bayesian network meta-analysis, which will be the most comprehensive evaluation of evidence to resolve the inconsistency among previous studies.

**Methods and analyses:** SSRIs including citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline and vilazodone have been selected. Systematic database searching and screening will be conducted for the RCTs on drug treatment of patients with MDD according to pre-specified search strategies and selection criteria. PubMed, the Cochrane Library, EMBASE, ScienceDirect, the US Food and Drug Administration Website, ClinicalTrial.gov and WHO Clinical Trials will be searched. Outcome data including Hamilton Depression Rating Scale (HDRS), Montgomery-Åsberg Depression Rating Scale (MADRS) and Clinical Global Impression (CGI) from eligible RCTs will be extracted. The outcomes will be analysed as ORs and mean differences under a random-effects model. A Bayesian network meta-analysis will be conducted with WinBUGS software, to compare the efficacies of SSRIs. Subgroup and sensitivity analysis will be performed to explain the study heterogeneity and evaluate the robustness of the results. Meta-regression analysis will be conducted to determine the possible factors affecting the efficacy outcomes. The Cochrane risk of bias assessment tool will be used to assess the RCT quality, and the Grading of Recommendation, Assessment, Development and Evaluation will be used to assess the strength of evidence from the meta-analysis.

**Ethics and dissemination:** No ethical approval is required because this study includes neither confidential personal patient data nor interventions with patients.

**Protocol registration number:** CRD42015024879.

## Strengths and limitations of this study

- Comprehensive Bayesian network meta-analysis using both BUGS and STAN models together with sensitivity analysis, subgroup analysis and meta-regression analysis will be conducted to evaluate the efficacies of selective serotonin reuptake inhibitors (SSRIs).
- This study will provide evidence to resolve the controversy over SSRI efficacy. This study will provide the latest findings to update current clinical guidelines for treating major depressive disorder.
- This study is inherently a retrospective meta-analytic study on randomised controlled trials only.

## INTRODUCTION

Major depressive disorder (MDD) is characterised by clear-cut changes in affect, cognition and neurovegetative functions and inter-episode remissions for at least 2 weeks, according to the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5).<sup>1</sup> Twelve-month prevalence of MDD in the USA was estimated to be about 7%, with marked differences by age group such that the prevalence in 18–29-year-old individuals is threefold higher than that in individuals aged 60 years or older.<sup>1</sup> Costs related to MDD were estimated to be US\$83 billion<sup>2</sup> and the projected loss of workforce productivity was up to US\$24 billion annually in the USA.<sup>3</sup> Surveys in the UK have found the prevalence in general practitioner practice attendees ranging from 3.5% in Aberdeen<sup>4</sup> to 5.6% in southern England.<sup>5</sup> According to the WHO,<sup>6</sup> MDD will be the largest worldwide contributor to disease burden by 2030.

Current clinical guidelines<sup>7–9</sup> recommended selective serotonin reuptake inhibitors (SSRI), including citalopram, escitalopram, fluoxetine,

fluvoxamine, paroxetine, sertraline and vilazodone, as the primary pharmacotherapy of MDD, based on some findings from previous randomised controlled trials (RCT)<sup>10–12</sup> and meta-analyses.<sup>13–26</sup> However, the previous RCTs and meta-analyses were critically inconsistent in efficacy findings. For instance, GlaxoSmithKline's Study 329 demonstrated the antidepressant paroxetine to have remarkable efficacy and safety in treatment of MDD in adolescence,<sup>10</sup> while a re-analysis found the antidepressant paroxetine neither safe nor effective.<sup>13</sup> An RCT found no significant difference in efficacy between sertraline and placebo groups,<sup>11</sup> but a multiple-treatment meta-analysis favoured sertraline over many antidepressants including other SSRIs. Sertraline was then deemed as the best choice for treating moderate-to-severe depression in adults.<sup>14</sup> A randomised, double-blind, placebo-controlled trial<sup>12</sup> demonstrated a large and significant treatment effect, and statistically significant depressive symptom improvements among patients taken vilazodone, while a prior study<sup>15</sup> found that the remission rates for vilazodone were not significantly different from placebo according to a systematic review on vilazodone in treating MDD. The data on clinical trials for efficacy conducted for marketing approval and submitted to the Food and Drug Administration showed that drug-placebo differences in antidepressant efficacy were small.<sup>16</sup> Selective publication of antidepressant trials also biased a few meta-analyses for efficacy determination.<sup>17–18</sup> Meanwhile, the evidence based on meta-analyses was neither statistically significant nor did it favour any particular second-generation

antidepressant, including SSRIs.<sup>19–26</sup> Available evidence showed no clear differences between the efficacy of immediate-release and extended-release antidepressants including three SSRIs (fluoxetine, fluvoxamine and paroxetine) in treating MDD.<sup>24</sup> This situation can be improved by a more methodically extensive network meta-analysis. As such, a protocol of a network meta-analysis of RCTs was published, aiming to reanalyse the efficacy, tolerability, acceptability and suicide risk of both first-generation and newer-generation antidepressants.<sup>25</sup> However, this protocol focused on the treatment of children and adolescent depression,<sup>25</sup> and a broader view to include adult depression would be desirable. Without proper evidence to support SSRI efficacy, a recent meta-regression study<sup>26</sup> determined the dose-dependence in treating MDD and found minimal benefits of SSRIs over placebo. Therefore, the issue about whether SSRIs are efficacious should be addressed by an improved network meta-analysis performed to rectify all known biases (table 1). The past meta-analyses performed neither sensitivity nor subgroup analyses adequately. Furthermore, only two<sup>19–21</sup> of the past meta-analyses evaluated the strength of evidence by the Grading of Recommendation, Assessment, Development and Evaluation (GRADE).<sup>27</sup>

## OBJECTIVES

This study aims to compare the efficacy of citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline,

**Table 1** Summary of included meta-analyses

Study	PMA	NMA	GRADE	Subgroup and sensitivity analyses	Meta-regression	No of SSRIs included	Placebo included	No of studies included
Ref 13	√	√	×	①②	⑩	6	0	49
Ref 14	×	×	×	③	×	1	1	8
Ref 15	√	×	×	④	×	2	1	35
Ref 16	√	×	×	⑤	×	5	1	74*
Ref 18	√	√	√†	③⑥⑦⑧⑨	×	6	1	>50‡
Ref 20	√	√	√†	③⑥⑦⑧⑨	√ (no result)	6	1	>40‡
Ref 21	√	×	×	④⑥⑧	×	6	1	21
Ref 22	√	×	√	⑥⑦⑧⑩⑪	×	6	1	18
Ref 23	×	√	×	⑰	×	3	1	94
Ref 24	×	√	×	⑪⑫	③⑤⑦⑧⑩⑫⑬	NA§	Unclear	NA§
Our protocol	×	√	√	①③⑤⑥⑦⑧⑨⑩⑪⑫⑬⑭⑮⑯⑰	①③⑤⑦⑧⑩⑪⑫⑬	7	1	≈120¶

①, dosage; ②, imputation; ③, phases treatment; ④, random- and fixed-effects models; ⑤, published and unpublished studies; ⑥, accompanying symptoms; ⑦, age; ⑧, sex; ⑨, ethnicity; ⑩, funding or sponsorship; ⑪, risk of bias; ⑫, sample sizes; ⑬, baselines of outcome measures; ⑭, severity of MDD; ⑮, RCT registered; ⑯, the DSM versions; ⑰, immediate-release versus extended-release formulations, ⑱, mechanism of action.

\*74 included studies on 12 new-generation antidepressants.

†Modified GRADE in which 8 factors in GRADE were divided into required domains including 4 factors and additional domains including 4 factors.

‡Estimation number of studies included.

§NA is not available because Ref 24 is a protocol.

¶Estimation number of eligible studies according to the current study searching.

×, non-conducted; √, conducted; GRADE, the Grading of Recommendation, Assessment, Development and Evaluation; NMA, network meta-analysis; PMA, pairwise meta-analysis; SSRIs, selective serotonin reuptake inhibitors.

vilazodone and placebo in treating MDD, using a comprehensive Bayesian network meta-analysis on RCTs.

## METHODS AND ANALYSIS

### Design

Systematic review and Bayesian network meta-analysis.

### Information sources

RCTs will be searched from PubMed, EMBASE, the Cochrane Library, ScienceDirect and PsycInfo. The following sources also will be searched for the grey literature: the US Food and Drug Administration Website, ClinicalTrials.gov and WHO Clinical Trials.

### Search strategies

Drug names, major depressive disorder and 'random\*' will be used as keywords to search titles or abstracts for eligible RCTs from selected databases. The search strategy was tested from March to August 2015. As an example, the following search strategy will be used for searching RCTs of citalopram for treating MDD in PubMed:

1. citalopram
2. major depressive disorder
3. random\*
4. 1 in Title or Abstract
5. 2 in MeSH Terms
6. 3 in Title or Abstract
7. 4 and 5 and 6

### Eligibility criteria

The retrieved reports will be screened according to the eligibility criteria shown below including participants, interventions, controls, outcome measures, types of study and other criteria.

#### ► Participants

Inclusion: participants must be adults aged at least 18 years and suffering from MDD diagnosed using DSM criteria.

Exclusion: participants suffering from other depressive disease conditions or diagnosed using other criteria or aged 18 years or pregnant woman.

#### ► Interventions

Inclusion: any RCT that evaluates the efficacy of selected SSRIs.

Exclusion: any RCT that evaluates other drugs or combined treatments of multiple drugs.

#### ► Controls

Inclusion: any RCT that evaluates the efficacy of a selected drug other than the drug of intervention. Exclusion: any RCT that evaluates other drugs or combined treatments of multiple drugs.

#### ► Outcome measures

Inclusion: efficacy outcome measures include mean difference of changes on the Hamilton Depression Rating Scale (HDRS), or Montgomery-Åsberg Depression Rating Scale (MADRS), or the Clinical Global Impression

(CGI), and treatment response in terms of the proportion of the participants who have 50% or greater improvement under the treatment, or the mean difference of scores according to HDRS or MADRS, or who receive much improved or very much improved scores in CGI.<sup>1</sup> The primary outcome measures are HDRS or MADRS improvement and the secondary outcome measure is CGI improvement from baseline to study end.<sup>22 28</sup>

Exclusion: other outcome measures.

#### ► Types of study

Inclusion: only RCTs will be included.

Exclusion: observational cohort and case-control studies, case reports, experimental studies and reviews will be excluded.

#### ► Other criteria

Other inclusion criteria: the RCTs must report complete efficacy data of HDRS, MADRS or CGI of each treatment. Follow-up periods must be at least 6 weeks. Other exclusion criteria are duplicated studies or studies of combined treatments with multiple drugs.

### Study selection

Reviewers will screen the retrieved database records independently according to the eligibility criteria. Disagreements between reviewers will be resolved by consensus. Selection process of studies will be shown in a PRISMA-compliant flow chart<sup>29</sup> (figure 1).

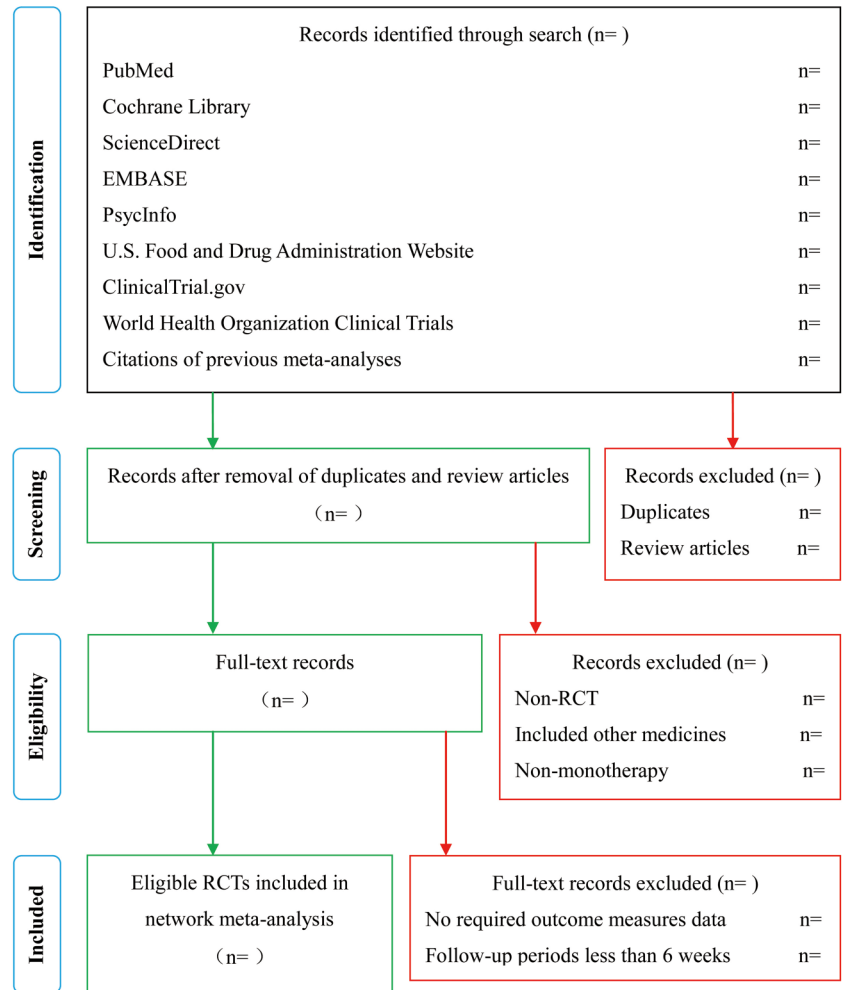
### Data extraction and quality assessment

Data of the study characteristics and the clinical outcome measures will be extracted. The data extracted from the RCTs are: (1) treatment outcome measures including HDRS, MADRS and CGI, (2) sample sizes, (3) follow-up periods, (4) dosages of interventions, (5) baselines of outcome measures, (6) phases of treatment, (7) interventions, (8) sponsorship or funding, (9) severity of MDD, (10) RCT registered, (11) accompanying symptoms, (12) the DSM versions, etc. The data will be standardised for comparability (table 2). The quality of eligible studies will be evaluated according to the Cochrane Collaboration's risk of bias tool<sup>30</sup> (table 3).

### Statistical analysis

The overall effect sizes will be determined as mean difference for continuous outcomes and ORs for dichotomous outcomes with their 95% credible intervals. Network meta-analysis based on the Bayesian hierarchical model<sup>31 32</sup> of included RCTs will be conducted. The differences in clinical and methodological characteristics among RCTs will be explored by subgroup analysis and sensitivity analysis. Subgroup analysis and sensitivity analysis will also be performed to evaluate the robustness of the results. Meta-regression analysis will be conducted to determine the possible factors affecting the efficacy. All drug effect parameters will be given flat normal (0, 0.0001) priors and the between-studies SD will be given flat, uniform (0, 5) distributions. A burn-in of 20 000 simulations will be discarded. All results are based on a

**Figure 1** Process of searching and screening studies. RCT, randomised controlled trial.



further sample of 80 000 simulations. Variances and consistencies among all comparisons will be assessed using the Brooks-Gelman-Rubin method under a random-effects model. Model fitness will be assessed with the deviance information criterion (DIC) and the posterior mean of the total residual deviance.<sup>33</sup> Bayesian inferences will be computed using a Markov-chain Monte Carlo simulation with WinBUGS, V.1.4.3 (Medical Research Council Biostatistics Unit, Cambridge, UK).<sup>34</sup> The strength of evidence from meta-analyses for outcome measures and major comparisons will be evaluated using the GRADE approach.<sup>27</sup> The overall ranking will be determined by the overall effect sizes. Mann-Whitney-Wilcoxon test, Kendall rank correlation and intraclass correlation

coefficient will be performed with statistical software R (R Development Core Team. R: a language and environment for statistical computing. Reference index version 2.12.0. R Foundation for Statistical Computing, Vienna, Austria. 2008) to determine the agreement among the rankings based on different outcome measures and subgroup analyses. A p value lower than 0.05 will be considered statistically significant.

## ETHICS AND DISSEMINATION

### Ethical issues

No ethical approval is required because this study includes neither confidential personal data nor interventions with patients.

**Table 2** Summary of the included RCTs

Study	Follow-up period	Sample size	Severity	Dosages	HDRS	MADRS	CGI	Sponsorship	...
RCT 1									
RCT 2									
RCT 3									
RCT 4									
RCT 5									

CGI, Clinical Global Impression; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; RCT, randomised controlled trial.

**Table 3** RCT quality assessment according to the Cochrane Collaboration's risk of bias tool

	RCT 1	RCT 2	RCT 3	RCT 4	RCT 5	...
Random sequence generation						
Allocation concealment						
Blinding of participants and personnel						
Blinding of outcome assessment						
Incomplete outcome data						
Selective reporting						
Other sources of bias						

Each item of an included RCT is evaluated at low risk, unclear risk and high risk of bias.

## Publication plan

This protocol has been registered (registration number: CRD42015024879) with the PROSPERO (International Prospective Register of Systematic Reviews).<sup>35</sup> The procedures of this systematic review and network meta-analysis will be conducted in accordance with the PRISMA-compliant guideline. The results of this network meta-analysis will be submitted to a peer-reviewed journal for publication.

**Contributors** S-wL conceived the study. YJ, HZ and S-wL wrote the protocol and approved the final manuscript.

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**Competing interests** None declared.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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